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Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large US Cohort

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List of abbreviations:

ALT: alanine aminotransferase
AST: aspartate aminotransferase
BMI: body mass index
CK: creatine kinase
COVID-19: coronavirus disease 19
CRP: C-reactive protein
ED: emergency department
HBV: hepatitis B virus
HCV: hepatitis C virus
Hgb: hemoglobin
HS troponin: high sensitivity troponin
HTN: hypertension
ICU: intensive care unit
IL-6: interleukin-6
INR: international normalized ratio
LDH: lactate dehydrogenase
NAFLD: nonalcoholic fatty liver disease
NASH: nonalcoholic steatohepatitis

PBC: primary biliary cholangitis
PSC: primary sclerosing cholangitis
ULN: upper limit of normal
WBC: white blood cell count

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Background & aims: Coronavirus disease 2019 (COVID-19) has been associated with acute liver injury manifested by increased liver enzymes in reports worldwide. Prevalence of liver injury and associated clinical characteristics are not well-defined. We aim to identify the prevalence of and risk factors for development of COVID-19 associated acute liver injury in a large cohort in the United States.

Approach & results: In this retrospective cohort study, all patients who underwent SARS-CoV-2 testing at three hospitals in the NewYork-Presbyterian network were assessed. Of 3381 patients, 2273 tested positive and had higher initial and peak ALT than those who tested negative. Acute liver injury was categorized as mild if alanine aminotransferase (ALT) was > upper limit of normal (ULN) but < two times ULN, moderate if ALT was between two and five times ULN, and severe if ALT was > five times ULN. Among patients who tested positive, 45% had mild, 21% moderate, and 6.4% severe liver injury. In multivariable analysis, severe acute liver injury was significantly associated with elevated inflammatory markers including ferritin (OR 2.40, $p<0.001$) and IL-6 (OR 1.45, $p=0.009$). Patients with severe liver injury had a more severe clinical course, including higher rates of ICU admission (69%), intubation (65%), renal replacement therapy (33%), and mortality (42%). In multivariable analysis, peak ALT was significantly associated with death or discharge to hospice (OR

1.14, p=0.044), controlling for age, body mass index, diabetes, hypertension, intubation, and renal replacement therapy.

Conclusion: Acute liver injury is common in patients who test positive for SARS-CoV-2, but is most often mild. However, among the 6.4% of patients with severe liver injury, a severe disease course should be anticipated.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic now includes over five million confirmed cases worldwide with an average mortality rate approaching 6.5%.(1) In the United States, New York City has over 195,000 cases and over 21,000 confirmed or suspected deaths.(1) COVID-19, the clinical syndrome caused by SARS-CoV-2, is primarily a respiratory disease leading in some to respiratory failure.(2) However, COVID-19 also has significant systemic manifestations including acute kidney injury, myocarditis, thrombosis, and acute liver injury.(2–10)

While the impact of COVID-19 on the liver remains poorly characterized, a significant proportion of patients with liver enzyme elevations have been reported. Although elevations in transaminases are most often mild [1-2 times the upper limit of normal (ULN)], severe liver injury has been reported. In addition, patients with severe COVID-19 may be more likely to have liver injury than patients with less severe disease or asymptomatic carriers.(2,4,5,11) While cholestasis and liver synthetic function abnormalities appear to be rare, hypoalbuminemia is emerging as a consistent risk factor for severe disease, even among patients without chronic illness.(5,10,11)

Emerging data suggests that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations are common among COVID-19 patients in the United States as well, with AST and ALT elevations found in 38-63% and 29-39% of patients, respectively.(12,13) Interestingly, American patients may have higher admission transaminase elevations compared to previously published data, highlighting the potential geographic variability in COVID-19 related liver injury.(14)

The mechanism by which SARS-CoV-2 impacts the liver is not fully understood, but is thought to be a combination of direct virally-mediated injury as well as the immune-mediated inflammatory response.(15) The SARS-CoV-2 cellular receptor, the angiotensin-converting enzyme 2 (ACE2) receptor, is present in biliary and hepatic endothelial cells, providing a plausible mechanistic explanation for the observed liver injury.(2,16,17) Among hospitalized patients, additional etiologies of liver injury must be considered including drug-induced liver injury, sepsis, shock, congestion, and extrahepatic sources of AST.(15)

Several risk factors for severe COVID-19 have been identified including advanced age, hypertension, diabetes, and obesity, however little is known about risk factors and the clinical course for patients with significant liver injury due to COVID-19. Our aim is to describe the prevalence of and risk factors for development of acute liver injury in patients with COVID-19, as well as investigate impact of acute liver injury on patient outcomes.

Methods:

Study design and participants:

Consecutive patients at the Columbia University Irving Medical Center, Morgan Stanley Children's Hospital and Allen Hospital sites of NewYork-Presbyterian Hospital who had a test for SARS-CoV-2 infection between March 8th and April 14th 2020 were retrospectively enrolled. All outcomes were assessed on May 18th, providing a minimum of 5 weeks of potential observation. Testing locations included outpatient clinics, the emergency department and inpatient locations at these institutions. This study was approved by the Columbia University Irving Medical Center Institutional Review Board.

SARS-CoV-2 infection was defined by detection of the virus using reverse-transcriptase PCR via Roche 6800 platform of nasopharyngeal swab specimens. For patients with multiple SARS-CoV-2 tests, if any test was positive the patient is included in the positive group, and the first positive test was used for the purposes of this analysis. Laboratory values including liver enzymes from the time of the SARS-CoV-2 test until discharge or death were obtained through automated data extraction tools. Patients without any liver chemistry results were excluded.

These data were utilized to describe the initial and peak AST and ALT encountered in patients with positive and negative testing. Among patients who tested positive, liver injury was then categorized by degree of ALT elevation as none/mild (<2 times ULN), moderate (2-5 times ULN) and severe (>5 times ULN). ALT was selected to represent liver injury rather than AST due to the more predominant extra-hepatic sources of AST rendering it less liver-specific. Measures of synthetic dysfunction including INR and bilirubin were not included in this definition given the multifactorial reasons for abnormal values in this clinical setting.

Clinical characteristics and comorbidities of patients with liver injury were examined. The presence of comorbidities, including the presence and etiology of liver disease, were determined by extraction of ICD-9 and 10 codes from the medical record. The association of category of liver injury with clinical outcomes was then assessed.

Analytic Approach

Median values of ALT were compared between patients with positive vs. negative SARS-CoV-2 testing using rank-sum. The proportion of patients with ALT <2 times the upper limit of normal (ULN), 2-5 times ULN and >5x ULN were compared between those with positive vs. negative SARS-CoV-2 testing using chi-square.

The ULN in our health care system is defined as 50 U/L for ALT and 37 U/L for AST.

The initial breakdown in proportions of patients with and without SARS-CoV-2 who had elevations in liver enzymes was then repeated utilizing the more conservative cutoffs for ALT of 19 U/L for women and 30 U/L for men.(18)

Patients with a positive test for SARS-CoV-2 were evaluated in subsequent analyses, categorized into those with peak ALT consistent with no/mild liver injury (<2 times ULN), moderate liver injury (2-5 times ULN) and severe liver injury (>5 times ULN). Continuous variables were compared across these categories with rank-sum and proportions with chi square analysis. Multivariable logistic regression was utilized to identify predictors of severe liver injury as well as the severe clinical outcomes of death or discharge to hospice. Continuous variables were log-transformed for logistic regression modeling. All covariates that were significant with $p<0.05$ in univariable analysis were

included in the final multivariable models. As BMI was not linear, it was dichotomized to above or below 35.

Results:

Impact of SARS-CoV-2 Positivity on Liver Enzymes

A total of 6913 patients were tested for SARS-CoV-2 infection in the study period, 3381 of whom had any ALT available and were included in this analysis. Of these 3381 patients, 2273 tested positive for SARS-CoV-2 and 1108 tested negative. The overall median (IQR) observation time from testing until death, discharge or last observation was 6 (3-13) days and all patients were eligible for at least 5 weeks of follow up from testing until this analysis.

Patients who tested positive for SARS-CoV-2 had higher median ALT values compared with patients who tested negative, including initial (28 U/L vs. 21 U/L, p<0.001) and peak (45 U/L vs. 25 U/L, p<0.001) values (Table 1). An ALT peak > ULN (45% vs. 26%, p<0.001) and > two times ULN (22% vs. 12%, p<0.001) were also more common among patients with a positive test compared to negative. Peak ALT > five times ULN was not significantly different between groups (6.4% positive vs. 5.0% negative, p=0.12).

When more conservative cutoffs for ALT of 19 U/L for women and 30 U/L for men are used, peak ALT > ULN (76% vs. 52%, p<0.001), > twice ULN (45% vs. 26%, p<0.001) and > five times ULN (16% vs. 9.5%, p<0.001) were significantly more common among patients who tested positive compared to negative (Supplemental Table 1).

Clinical Characteristics of Patients with SARS-CoV-2 and Liver Enzyme Elevation

The clinical characteristics of the 2273 patients who tested positive for SARS-CoV-2 are presented in Table 2. The overall median age at time of testing was 65, 57% were men, 50% were of Hispanic/Latino ethnicity, 23% were white, and 21% were black. Overall, patients with evidence of severe liver injury were younger (p<0.001) and more likely to be male (p<0.001).

The rates of medical comorbidities by the category of peak ALT elevation are displayed in Table 2. Hypertension and diabetes were the most common comorbidities, and both were inversely

associated with a higher category of peak ALT elevation (p<0.001). Chronic kidney disease was associated with a higher category of peak ALT elevation (p<0.001).

Overall, 5.0% of patients had chronic liver disease, 1.4% with advanced fibrosis or cirrhosis. The most common etiologies of underlying liver disease included hepatitis C virus (HCV), non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), hepatitis B virus (HBV), and alcohol-related liver disease. None of these baseline chronic liver diseases were significantly associated with category of liver injury.

Correlation between Liver Enzymes and Laboratory Markers of Liver Function and Inflammation

The median peak AST and ALT among patients with severe liver injury were 697 U/L and 444 U/L, respectively (Table 3). Initial and nadir albumin levels were significantly lower in patients with severe liver injury (p=0.009 and p<0.001, respectively). Although initial alkaline phosphatase levels were similar across all categories of ALT, median peak value was higher in patients with severe liver injury (p<0.001), however it was only mildly elevated. Initial total bilirubin was higher in patients with severe livery injury, although still in the normal range (p<0.001); however, the median peak total bilirubin was modestly elevated up to 1.50 in the severe liver injury group. Only 1.9% of patients in the entire cohort had total bilirubin >5 mg/dl*.* Similarly, median initial INR was in the normal range for all groups, however there was a significant but modest elevation in peak INR among the severe liver injury group at 1.5 (p<0.001). Severe liver injury was also associated with a significantly higher white blood cell count and neutrophil-to-lymphocyte ratio (NLR) (both p<0.001).

Finally, severe liver injury was associated with markers of end organ dysfunction including peak levels of high sensitivity (HS) troponin, creatine kinase, and serum creatinine, as well as inflammatory markers including peak procalcitonin, C-reactive protein (CRP), D-Dimer, ferritin and interleukin-6 (IL-6) levels (all p<0.001).

Predictors of Severe Liver Injury

Univariable and multivariable logistic regression was performed to identify predictors of severe liver injury with peak ALT > five times ULN (Table 4). In the final multivariable model, serologic inflammatory markers including peak ferritin (OR 2.40, p<0.001) and peak IL-6 (OR 1.45, p=0.009)

were significantly associated with severe liver injury, controlling for age, sex, and peak levels of D-dimer, C-reactive protein, procalcitonin, creatine kinase and high sensitivity troponin.

Clinical Outcomes

Overall, the highest level of care required was outpatient only in 12 (0.5%), discharged from the Emergency Department in 92 (4.1%), inpatient admission in 1640 (72%), and ICU care in 529 (23%) (Table 5). Moderate and severe acute liver injury was more common in patients who required ICU-level care ($p<0.001$). Among the 92 patients discharged from the ED, 93% had an ALT <two times ULN. Among the 529 patients who required ICU-level care, 54% had an ALT <two times ULN, 27% had an ALT 2-5 times ULN, and 19% had an ALT >five times ULN.

Severe clinical outcomes were also more common among patients with severe liver injury. At the time of this analysis, with a minimum of 5 weeks of potential observation time, patients with severe liver injury were significantly more likely to have been intubated compared to moderate or no/mild liver injury (65% vs. 38% vs. 13%, $p<0.001$), to have required renal replacement therapy (33% vs. 15% vs. 7.5%, $p<0.001$), and to have died in the hospital (42% vs. 23% vs. 21%, $p<0.001$).

When looking specifically at the 145 patients with severe liver injury, most had a severe COVID-19 course. Of these patients, 69% required ICU-level care, 65% were intubated, 70% required vasopressors, 12% inotropes and 33% renal replacement therapy during their hospitalization. 39% of patients were paralyzed, 10% proned, and 4 required extracorporeal membrane oxygenation (ECMO). The most common COVID-19 targeted therapy given was hydroxychloroquine (76%), followed by corticosteroids (49%), tocilizumab (26%), sarilumab (6.2%), and remdesivir (4.8%). Of 7 patients who received remdesivir, 29% had peak ALT before medication, 29% had peak ALT within 7 days of medication, and 42% had peak ALT after 7 days from medication dose. Of 46 patients who received tocilizumab or sarilumab, 17% had peak ALT before medication, 44% had peak ALT within 7 days of medication, and 39% had peak ALT after 7 days from medication dose.

Predictors of Death or Discharge to Hospice

Univariable and multivariable analysis was then performed to identify predictors of death or discharge to hospice (Table 6). In the final multivariable model, peak ALT was significantly associated with this severe outcome (OR 1.14, $p=0.044$), as were older age (OR 1.07, $p<0.001$),

diabetes (OR 1.30, p=0.045) and intubation (OR 4.77, p<0.001), controlling for BMI, hypertension, and the use of renal replacement therapy.

Discussion:

Liver injury, as manifested by ALT and AST elevation, is emerging as a clinically important consequence of COVID-19, and may predict a severe disease course. In this cohort with 2273 cases and 1108 controls, we demonstrate that initial and peak ALT are higher in those who test positive for SARS-CoV-2 compared to those who test negative with a similar clinical presentation. However, the overall median initial and peak levels of liver enzymes were mildly elevated with <2 times ULN in the majority of patients, even in this largely inpatient setting. Overall, moderate liver injury (peak ALT 2-5 times the ULN) was present in 22% and severe liver injury (peak ALT over 5 times ULN) in 6.4% of the COVID-19 cohort. Severe elevation in peak ALT was not significantly more common in SARS-CoV-2 positive patients compared with SARS-CoV-2 negative patients when using our local ULN value, though was significantly elevated when using the more conservative ULN of 19 for women and 30 for men.

The prevalence of liver enzyme elevation observed here is similar to what has been reported in large cohorts in China, where the prevalence has ranged from 3.75% to 53.1%, but most reporting a prevalence of ~20-30%.(19) While definitions of liver injury have been variable in the literature to date, here we used ALT cutoffs as defined by our local ULN, which are higher than the conservative cutoffs endorsed by the American Association for the Study of Liver Diseases.(18) While when looking at these more conservative cutoffs, the prevalence of enzyme elevations was higher, our overall conclusions regarding the impact of COVID-19 on the prevalence of elevated liver enzymes did not significantly change.

As in other reports, we observed a largely hepatocellular pattern of liver injury with few patients with elevated bilirubin and/or elevated alkaline phosphatase, even in the severe liver injury category. The mechanism of liver injury remains largely unknown and is thought to be a combination of both direct virally-mediated effects as well as a result of the immune response.(15) Only limited cases of hepatic histology have been reported, though it is known the ACE2 receptor is present on biliary epithelial cells(16), so it is interesting that bilirubin was often normal even in extreme cases. Given the emerging impact of COVID-19 on coagulation, including clinical observations of thrombosis and

disseminated intravascular coagulation, INR as a measure of synthetic function was not included in our definition of liver injury. Yet, only mild elevations in INR were seen even in the most severe cases. However, significant hypoalbuminemia was observed, particularly among patients with severe liver injury.

Several clinical characteristics were significantly associated with severe liver injury, including younger age and male sex. Interestingly, despite being associated with poor outcomes, severe liver injury was inversely associated with the presence of hypertension and diabetes. It is possible that younger patients mount a more robust immune and inflammatory response to infection, and that higher peak ALT is a manifestation of this response. This is supported by the fact that younger age, peak IL-6 and peak ferritin were the strongest predictors of severe liver injury in multivariable modeling.

Overall, 5% of patients in our cohort had chronic liver disease, 1.4% with advanced fibrosis or cirrhosis. This is a higher rate than has been reported in recent data from other cohorts, and the clinical course of COVID-19 among patients with chronic liver disease or cirrhosis is not known. The presence of chronic liver disease, advanced fibrosis or cirrhosis, and type of liver disease (including NAFLD, HCV and HBV) were not significantly associated with category of liver injury, which may be due in part to the overall low numbers of patients with these disease entities. While the prevalence of NAFLD in this cohort may be underreported due to the ICD-based diagnosis, it is notable that metabolic risk factors including BMI >35, diabetes, and hypertension were not associated with severe liver injury. Although it is clear that additional study is needed on the impact of underlying liver disease on clinical outcomes including death, it does not appear that patients with NAFLD or other metabolic risk factors are at increased risk of an acute rise in liver enzymes as part of their course.

It is possible that some patients with severe COVID-19 had additional liver insults including ischemia, congestion and drug-induced liver injury. In addition, extrahepatic sources of AST are likely common in this scenario, including from heart and skeletal muscle breakdown, thus we focused on ALT in the majority of our analysis. However, it appears that ALT levels correlate well with markers of inflammation and are likely higher among patients with severe cytokine release syndromes.(4,7,10,11,13) This is supported by the significantly higher peak levels of all inflammatory markers among those with severe ALT elevation, including CRP, D-dimer, ferritin and IL-6. IL-6 in

particular has been described as a possible marker for severe COVID-19 related disease.(20) In addition, cytokine storm syndromes have been described in COVID-19, and are associated with severe elevations in liver enzymes.(21) It is possible that severe ALT elevations correlate with the inflammatory response to the virus.

Higher peak ALT values were also significantly associated with overall disease severity and measured clinical outcomes. Patients with severe liver injury were significantly more likely to have respiratory failure requiring intubation as well as renal failure requiring renal replacement therapy. Moreover, these patients were more likely to be admitted to the ICU and to have died in the hospital. When the 145 patients with severe liver injury were evaluated in more detail, many required vasopressors, and were treated with a broad range of COVID-19 treatment strategies including agents such as tocilizumab, sarilumab and remdesivir that have been associated with liver enzyme elevation. This highlights an important clinical challenge in these patients as those with elevated ALT are often excluded from clinical trials of these agents.

Limitations of this analysis include that this represents an almost exclusively inpatient population and includes a period in our center when only the sickest patients were tested in general. Therefore, this information may not be applicable to outpatients or those with mild disease. In addition, it was not possible to characterize all the possible additional sources of liver injury including the use of hepatotoxic medications, or to clearly attribute changes in parameters of liver synthetic function to liver injury alone. Finally, although all patients are eligible for a minimum of 5 weeks of follow up, some patients in this cohort remain hospitalized (5.7% intubated, 3.6% not intubated), including several with severe liver injury. Thus, the ultimate clinical outcomes are not yet known for the entire cohort, and many of these patients with prolonged intubated remain at risk of inpatient mortality. However, the final disposition is currently known in over 90% of the cohort, and given the overall large number of patients included, additional follow up is unlikely to change the overall conclusions significantly.

In summary, in this cohort of 3381 patients, acute liver injury was more common among the 2273 patients with confirmed SARS-CoV-2 than among those with a similar presentation who tested negative. However, severe liver injury with ALT peak greater than five times ULN occurred in only 6.4% of patients. These liver enzyme elevations were rarely associated with cholestasis, but did correlate with other markers of end organ injury as well as cytokines and markers of inflammation. Finally, severe liver injury was associated with the most severe clinical outcomes including death and may be a useful prognostic marker for hospitalized patients.

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Table 1: Initial and peak AST and ALT by SARS-CoV-2 test result

	SARS-CoV-2 Result			
	Overall (n= 3381)	**Positive (n= 2273)**	**Negative (n= 1108)**	**p-value**
Initial ALT, median (IQR)	26 (17, 46)	28 (18, 49)	21 (14, 37)	<0.001
Initial ALT (%)				
> ULN	736 (22)	537 (24)	199 (18)	<0.001
> 2x ULN	209 (6.2)	134 (5.9)	75 (6.8)	0.4
> 5x ULN	58 (1.7)	29 (1.3)	29 (2.6)	0.007
Peak ALT, median (IQR)	37 (21, 76)	45 (25, 89)	25 (17, 52)	<0.001
Peak ALT (%)				
ALT peak > ULN	1303 (39)	1015 (45)	288 (26)	<0.001
ALT peak > 2x ULN	624 (18)	489 (21)	135 (12)	<0.001
ALT peak > 5x ULN	200 (5.9)	145 (6.4)	55 (5.0)	0.12
Initial AST, median (IQR)	37 (23, 62)	43 (28, 69)	26 (18, 47)	<0.001
Initial AST (%)				
> ULN	1649 (49)	1280 (56)	369 (33)	<0.001
> 2x ULN	627 (19)	486 (21)	141 (13)	<0.001
> 5x ULN	135 (4.0)	87 (3.8)	48 (4.3)	0.5
Peak AST, median (IQR)	52 (29, 100)	62 (36, 115)	33 (21, 62)	<0.001
Peak AST (%)				
> ULN	2165 (64)	1671 (74)	494 (45)	<0.001
> 2x ULN	1180 (35)	950 (42)	230 (21)	<0.001
> 5x ULN	381 (11)	294 (13)	87 (7.9)	<0.001

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

Table 2: Patient demographics and comorbidities by category of peak ALT elevation among patients with positive test for SARS-CoV-2

	Overall (n= 2273)	ALT < 2x ULN (n= 1784)	ALT 2-5x ULN (n= 344)	ALT > 5x ULN (n= 145)	p-value
Age (years), median (IQR)	65 (52, 76)	66 (53, 78)	61 (50, 73)	63 (50, 71)	<0.001
Sex (%)					<0.001
Male	1297 (57)	949 (53)	242 (70)	106 (73)	
Female	976 (43)	835 (47)	102 (30)	39 (27)	
BMI (kg/m^2), median (IQR)					
BMI >35 (kg/m^2) (%)[1]	347 (17)	263 (17)	57 (18)	27 (20)	0.6
Hispanic/Latino Ethnicity (%)	1140 (50)	884 (50)	184 (53)	72 (50)	0.7
Race					
White	531 (23)	426 (24)	75 (22)	30 (21)	0.5
Black	478 (21)	387 (22)	66 (19)	25 (17)	0.3
Asian	20 (0.9)	15 (0.8)	2 (0.6)	3 (2.1)	0.2
Other/unknown	1274 (56)	984 (55)	202 (59)	88 (61)	0.2
Comorbidities (%)					
Hypertension	1375 (60)	1130 (63)	166 (48)	79 (54)	<0.001
Diabetes	886 (39)	738 (41)	100 (29)	48 (33)	<0.001
Chronic kidney disease	470 (21)	346 (19)	69 (20)	55 (38)	<0.001
Asthma	308 (14)	259 (15)	34 (9.9)	15 (10)	0.036
COPD	185 (8.1)	163 (9.1)	15 (4.4)	7 (4.8)	0.004
Pulmonary fibrosis	17 (0.7)	15 (0.8)	1 (0.3)	1 (0.7)	0.6
Any pulmonary disease	430 (19)	364 (20)	45 (13)	21 (15)	0.002
Chronic liver disease (%)	114 (5.0)	91 (5.1)	15 (4.4)	8 (5.5)	0.8
Advanced fibrosis or cirrhosis	31 (1.4)	27 (1.5)	3 (0.9)	1 (0.7)	0.7
Alcohol-related liver disease	12 (0.5)	8 (0.4)	3 (0.9)	1 (0.7)	0.4
NAFLD or NASH	44 (1.9)	33 (1.8)	5 (1.5)	6 (4.1)	0.14
Hepatitis B	15 (0.7)	11 (0.6)	3 (0.9)	1 (0.7)	0.6
Hepatitis C	44 (1.9)	35 (2.0)	8 (2.3)	1 (0.7)	0.5
Autoimmune hepatitis	2 (<0.1)	1 (<0.1)	0 (0)	1 (0.7)	0.15

PBC	2 (<0.1)	2 (0.1)	0 (0)	0 (0)	>0.9
PSC	5 (0.2)	5 (0.3)	0 (0)	0 (0)	>0.9
Hemochromatosis	4 (0.2)	3 (0.2)	1 (0.3)	0 (0)	0.6

[1]N=2026

Abbreviations: BMI = body mass index, CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; HTN = hypertension; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; PBC = primary biliary cholangitis; PSC = primary sclerosing cholangitis

Table 3: Laboratory data by category of peak ALT elevation among patients with positive test for SARS-CoV-2

	Overall (n= 2273)	ALT < 2x ULN (n= 1784)	ALT 2-5x ULN (n= 344)	ALT > 5x ULN (n= 145)	p-value
Liver Enzymes and Function					
ALT U/L[1]					
Initial	28 (18, 49)	25 (17, 39)	54 (31, 97)	63 (30, 177)	<0.001
Peak	45 (25, 89)	34 (22, 56)	140 (120, 180)	444 (294, 923)	<0.001
AST U/L[1]					
Initial	43 (28, 69)	37 (26, 58)	66 (45, 109)	91 (51, 199)	<0.001
Peak	62 (36, 115)	50 (32, 77)	160 (112, 227)	697 (256, 1685)	<0.001
Total bilirubin mg/dl[2]					
Initial	0.50 (0.30, 0.70)	0.40 (0.30, 0.60)	0.50 (0.40, 0.70)	0.60 (0.40, 0.90)	<0.001
Peak	0.60 (0.40, 1.00)	0.60 (0.40, 0.80)	0.90 (0.60, 1.60)	1.50 (0.90, 3.00)	<0.001
Alkaline phosphatase U/L[2]					
Initial	78 (62, 104)	77 (62, 102)	78 (59, 107)	84 (59, 124)	0.2
Peak	95 (72, 142)	89 (70, 125)	126 (89, 219)	163 (108, 279)	<0.001
Albumin g/dl[2]					
Initial	3.70 (3.40, 4.10)	3.80 (3.40, 4.10)	3.70 (3.40, 4.00)	3.60 (3.30, 4.00)	0.009
Nadir	3.10 (2.60, 3.60)	3.20 (2.80, 3.70)	2.70 (2.20, 3.20)	2.30 (1.80, 2.90)	<0.001
INR[3]					
Initial	1.10 (1.00, 1.20)	1.10 (1.00, 1.20)	1.10 (1.00, 1.20)	1.20 (1.00, 1.30)	0.029
Peak	1.20 (1.10, 1.40)	1.20 (1.10, 1.30)	1.30 (1.20, 1.40)	1.50 (1.30, 2.20)	<0.001
Blood Counts					
WBC x1000/µl[4]	8.0 (5.9, 11.0)	7.5 (5.6, 10.3)	9.4 (7.1, 12.4)	12.5 (8.5, 15.8)	<0.001
Hgb g/dl[4]	12.09 (10.18, 13.50)	12.27 (10.43, 13.50)	11.73 (9.50, 13.57)	10.57 (8.95, 12.60)	0.001
Platelets x1000/µl[4]	231 (172, 302)	226 (170, 293)	270 (194, 323)	234 (166, 304)	<0.001
Neutrophil count/µl[5]	576 (398, 851)	535 (379, 800)	726 (487, 959)	872 (603, 1199)	<0.001
Lymphocyte count/µl[5]	111 (79, 148)	111 (80, 148)	110 (80, 151)	103 (75, 144)	0.7
Neutrophil-lymphocyte ratio[6]	5.6 (3.4, 9.3)	5.1 (3.2, 8.4)	6.8 (4.5, 11.4)	9.3 (5.8, 15.2)	<0.001
Additional Markers of Organ Damage and Inflammation					
Creatinine, mg/dl[7]					

Initial	1.07 (0.81, 1.62)	1.07 (0.80, 1.65)	1.03 (0.82, 1.52)	1.14 (0.80, 1.57)	0.6
Peak	1.31 (0.91, 2.65)	1.24 (0.88, 2.31)	1.42 (0.94, 3.29)	3.09 (1.26, 6.72)	<0.001
HS-Troponin ng/L[8]					
Initial	17 (8, 44)	18 (8, 44)	14 (7, 36)	18 (9, 65)	0.011
Peak	25 (10, 79)	23 (9, 64)	29 (10, 108)	104 (24, 258)	<0.001
CK[9]					
Initial	162 (77, 360)	148 (73, 322)	194 (92, 492)	229 (118, 499)	<0.001
Peak	216 (93, 579)	184 (81, 432)	350 (137, 1048)	502 (206, 2151)	<0.001
Procalcitonin ng/ml[10]					
Initial	0.23 (0.11, 0.60)	0.20 (0.10, 0.55)	0.30 (0.16, 0.75)	0.35 (0.16, 1.10)	<0.001
Peak	0 (0, 2)	0 (0, 1)	1 (0, 4)	3 (1, 18)	<0.001
CRP mg/L[11]					
Initial	116 (57, 202)	107 (49, 188)	155 (84, 257)	146 (92, 225)	<0.001
Peak	166 (80, 277)	147 (65, 246)	246 (139, 300)	262 (180, 300)	<0.001
D-Dimer ug/ml[12]					
Initial	1.5 (0.8, 3.2)	1.4 (0.8, 3.1)	1.7 (0.9, 3.6)	1.8 (0.9, 5.9)	0.002
Peak	2.5 (1.0, 10.8)	2.0 (1.0, 6.4)	5.3 (1.5, 20.0)	19.6 (3.9, 20.0)	<0.001
Ferritin ng/ml[13]					
Initial	694 (347, 1264)	614 (306, 1091)	1048 (551, 1982)	1056 (541, 2368)	<0.001
Peak	916 (435, 1879)	760 (359, 1402)	1621 (934, 2872)	3702 (1552, 10008)	<0.001
IL-6 Level pg/ml[14]					
Initial	21 (7, 51)	18 (6, 46)	27 (10, 59)	40 (16, 93)	<0.001
Peak	33 (10, 114)	25 (8, 73)	63 (19, 158)	158 (50, 158)	<0.001
LDH Level U/L[15]					
Initial	410 (299, 573)	379 (281, 525)	502 (379, 686)	576 (428, 892)	<0.001
Peak	472 (336, 688)	424 (313, 601)	617 (466, 842)	1148 (640, 2123)	<0.001

*All continuous variable represented as median (IQR)

*[1]N=2273, [2]N=2268, [3]N=2018, [4]N=2264, [5]N=2109, [6]N=2115, [7]N=2269, [8]N=2056, [9]N=1761, [10]N=2065, [11]N=2070, [12]N=1791, [13]N=2032, [14]N=1607, [15]N=2052

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CRP = C-reactive protein; Hgb = hemoglobin; HS-troponin = high sensitivity troponin; INR = international normalized ratio; LDH = lactate dehydrogenase; ULN = upper limit of normal; WBC = white blood cell count

Table 4: Multivariable predictors of peak ALT > 5x ULN among patients with positive test for SARS-CoV-2*

Covariate	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.99	0.97, 1.00	0.015	0.98	0.97, 1.00	0.058
Female sex	0.48	0.30, 0.74	0.001	0.84	0.50, 1.40	0.5
BMI > 35	0.75	0.47,1.23	0.2	0.71	0.40,1.28	0.2
Liver disease	1.33	0.54, 2.81	0.5			
Diabetes	0.87	0.58, 1.30	0.5			
Hypertension	0.95	0.64, 1.42	0.8			
Peak IL-06	2.16	1.77, 2.69	<0.001	1.45	1.10, 1.93	0.009
Peak ferritin	3.01	2.47, 3.72	<0.001	2.40	1.90, 3.08	<0.001
Peak D-Dimer	1.57	1.37, 1.82	<0.001	1.13	0.91, 1.39	0.3
Peak CRP	2.55	1.76, 3.94	<0.001	0.82	0.55, 1.33	0.4
Peak procalcitonin	1.48	1.35, 1.63	<0.001	0.99	0.84, 1.15	0.9
Peak creatine kinase	1.52	1.33, 1.73	<0.001	1.05	0.89, 1.24	0.5
Peak high sensitivity troponin	1.53	1.35, 1.75	<0.001	1.14	0.94, 1.37	0.2

*N=1176

Abbreviations: BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; OR = odds ratio

Table 5: Patient outcomes by category of peak ALT elevation among patients with positive test for SARS-CoV-2

	Overall (n= 2273)	ALT < 2x ULN (n= 1784)	ALT 2-5x ULN (n= 344)	ALT > 5x ULN (n= 145)	p-value
Highest level of care (%)					<0.001
Outpatient	12 (0.5)	11 (0.6)	1 (0.3)	0 (0)	
Discharged from ED	92 (4.1)	86 (4.8)	4 (1.2)	2 (1.4)	
Admitted	1640 (72)	1402 (79)	196 (57)	42 (29)	
ICU	529 (23)	285 (16)	143 (42)	101 (69)	
Intubated (%)	452 (20)	225 (13)	132 (38)	95 (65)	<0.001
Extubated (%)	99 (4.4)	58 (3.3)	25 (7.3)	16 (11)	<0.001
Renal replacement therapy (%)	231 (10)	133 (7.5)	50 (15)	48 (33)	<0.001
In-hospital mortality (%)	517 (23)	378 (21)	78 (23)	61 (42)	<0.001
Current disposition (%)					<0.001
Discharged	1530 (67)	1288 (72)	199 (58)	43 (30)	
Admitted (not intubated)	81 (3.6)	53 (3.0)	18 (5.2)	10 (6.9)	
Admitted (intubated)	130 (5.7)	51 (2.9)	48 (14)	31 (22)	
Deceased/Discharged to hospice	532 (23)	392 (22)	79 (23)	61 (42)	

Abbreviations: ED = emergency department; ICU = intensive care unit

Table 6: Multivariable predictors of death or discharge to hospice among patients with positive test for SARS-CoV-2

Covariate	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Peak ALT	1.22	1.10, 1.35	<0.001	1.14	1.00, 1.30	0.044
Age	1.07	1.06, 1.08	<0.001	1.07	1.07, 1.10	<0.001
Female sex	0.83	0.67, 1.02	0.077			
BMI >35	1.57	1.17, 2.13	0.003	1.06	0.75, 1.52	0.7
Diabetes	1.65	1.34, 2.02	<0.001	1.30	1.01, 1.68	0.045
Hypertension	2.43	1.92, 3.10	<0.001	1.15	0.85, 1.56	0.4
Liver disease	0.66	0.39, 1.07	0.11			
Intubation	3.39	2.70, 4.26	<0.001	4.77	3.49, 6.55	<0.001
Renal replacement therapy	1.90	1.41, 2.54	<0.001	1.30	0.90, 1.88	0.2

*N=2026

Abbreviations: ALT = alanine aminotransferase; BMI = body mass index; CI = confidence interval; OR = odds ratio